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TETRAHEDRON

Approaches to the D-E Ring of the Polyether Antibiotic Salinomycin Using Sharpless Asymmetric Dihydroxylation

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Abstract: The work described herein provides a model system for appendage of the E ring of *epi*-17-deoxy-(*O*-8)-salinomycin **3** onto bis-spiroacetal aldehyde **6**. The conversion of aldehyde **7** to bicyclic ether **8** *via* silver assisted ring expansion of the mesylate derived from tetrahydrofuran alcohol **33** is described. Attempts to provide a stereoselective synthesis of epoxide **27** required for the preparation of **33** and hence **8** are reported. Alcohol **9** was prepared by chelation controlled addition of the Grignard reagent derived from bromide **15** to aldehyde **7**. Bromide **15** in turn was prepared as a 9:1 *E:Z* mixture of isomers with the required *E*-stereochemistry being introduced *via* a stereoselective Julia ring opening of cyclopropane **20**. Sharpless asymmetric dihydroxylation of alkenes **10** and **11** readily provided diols **22** and **25** [or **23** and **26** respectively], however, their subsequent conversion to epoxides **27** and **30** with retention of stereochemistry proved unsuccessful. Cyclic sulfites **37, 39** and sulfates **42, 45** were investigated as epoxide equivalents. Base induced cyclization of sulfites **37, 39** only afforded triols **21, 24**. Analogous reaction using sulfates **42, 45** favoured endo cyclization to a tetrahydropyran ring, however, the acidic conditions required for hydrolysis of the initial alkyl sulfate effected undesired elimination of the resultant tertiary alcohol. Whilst a stereoselective synthesis of the correct epoxide **27** required for preparation of tetrahydropyran **8** *via* ring expansion of tetrahydrofuran **33** has not been achieved, these latter conversions have been successfully demonstrated by the conversion of epoxides **28** and **31** to a 1:1 mixture of tetrahydrofurans **33** and **34** which were separable by flash chromatography. Subsequent ring expansion of these tetrahydrofurans **33** and **34** to tetrahydropyrans **8** and **14** was effected upon treatment with methanesulfonyl chloride followed by silver carbonate.

INTRODUCTION

The polyether antibiotic salinomycin **1**[1] exhibits marked antimicrobial activity against Gram-positive bacteria, mycobacteria, and fungi. Salinomycin **1** and its congeners narasin A **2**[2] and *epi*-17-deoxy-(*O*-8)-salinomycin **3**[3] act as ionophores and are also used commercially as growth promotants for ruminants and for the treatment of coccidial infections in poultry. The tricyclic bis-spiroacetal core of salinomycin is one of the most complex ensembles in the polyether antibiotics and the construction of this moiety has stimulated several approaches to this unit. Kishi *et al.*[4] and Yonemitsu *et al.*[5] used an acid catalysed intramolecular ketalization of a bis-methylacetal to construct the desired heterocycle whereas Kocienski and Brown[6] constructed the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene unit by an oxidative rearrangement of a 2-acyl furan.

Our approach to the bis-spiroacetal moiety of *epi*-17-deoxy-(*O*-8)-salinomycin **3** resulted in development of an oxidative cyclization of an hydroxyspiroacetal **4** to a bis-spiroacetal **5** (Scheme 1).[7] Bis-spiroacetal **5** is a key intermediate for the synthesis of the polyether antibiotic *epi*-17-(*O*-8)-salinomycin **3**. It

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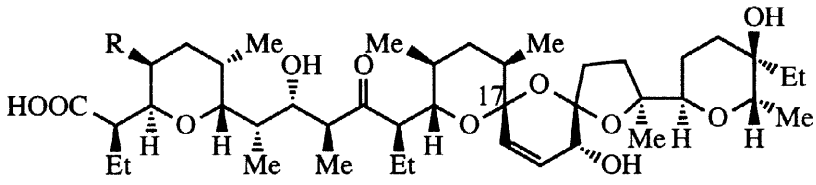
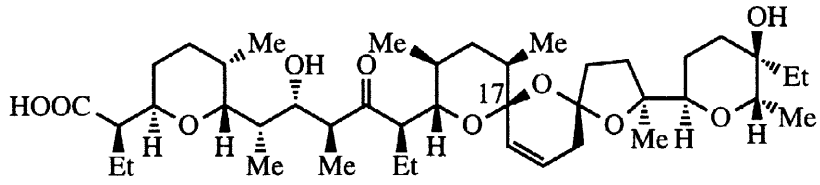
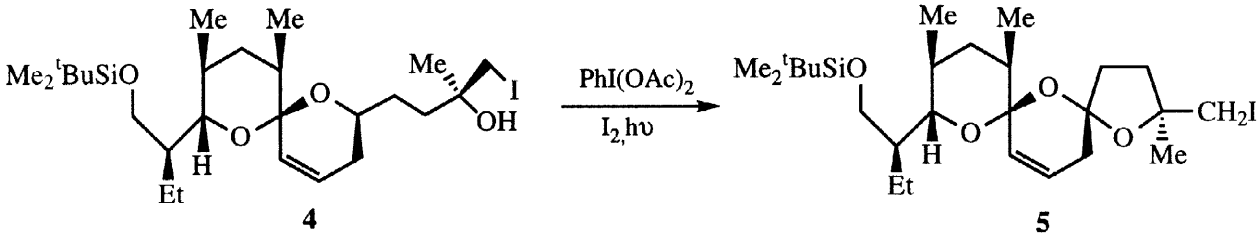
not only possesses the correct stereochemistry of the bis-spiroacetal system but it also contains functional groups at either end of the molecule providing "handles" to allow further elaboration to complete the synthesis of the natural product **3**.



Salinomycin **1** R=H
Narasin A **2** R=Me



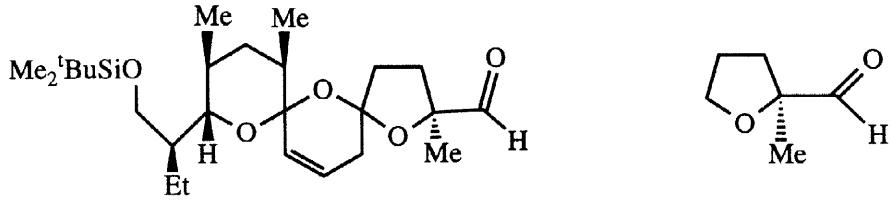
epi-17-Deoxy-(*O*-8)-salinomycin **3**



4 **5**

Scheme 1

Given that iodobis-spiroacetal **5** can be converted into aldehyde **6**, our synthetic approach to *epi*-17-deoxy-(*O*-8)-salinomycin **3** is now focused on attachment of the E ring to the BCD fragment. Towards this end, our attention has focused on a model system, namely, the conversion of the simpler aldehyde **7** to the bicyclic ether **8**. This is a worthwhile exercise given the number of steps involved to prepare bis-spiroacetal aldehyde **6**.

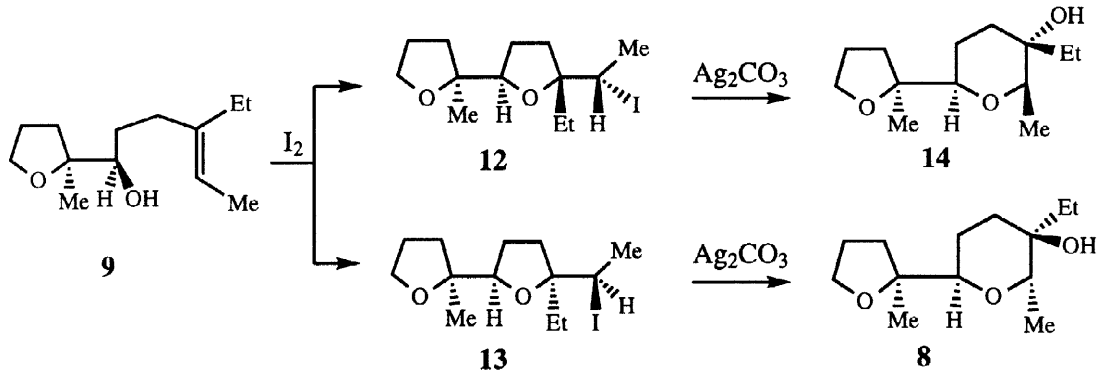


6 **7**

RESULTS AND DISCUSSION

We have previously reported an approach to bicyclic ether **8** *via* iodoetherification of bishomoallylic alcohol **9** followed by ring expansion (Scheme 2).[8] In this case the critical electrophilic cyclisation could not be induced to favour the iodoether **13** required for elaboration to bicyclic ether **8**, over iodoether **12** which

leads to the isomeric bicyclic ether **14**. The work described herein therefore focuses on the acid catalysed cyclization of hydroxyepoxide **27** to form alcohol **33** which upon mesylation undergoes ring expansion to the desired pyran **8**. Several polyether antibiotics e.g. lasalocid A[9], antibiotic X-206[10], ferensimycin B[11], and lysocellin[12] contain structural units similar to that present in **14** and **8** hence an efficient approach to these bicyclic ethers is of relevance to the synthesis of these polyether antibiotics.



Scheme 2

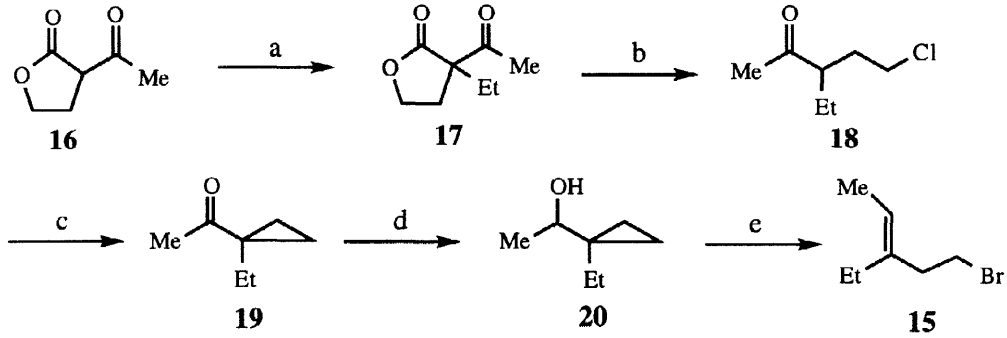
In the synthesis of lasalocid A by Kishi *et al.*,[13] epoxidation of a similar bishomoallylic alcohol led to stereoselective formation of the incorrect epoxide thereby necessitating an inelegant inversion of epoxide stereochemistry before acid catalyzed cyclization to the correct tetrahydrofuran. In the work described herein we therefore proposed the use of Sharpless asymmetric dihydroxylation to prepare the correct epoxide for subsequent cyclization.

Alcohol **9** was prepared from chelation controlled addition of the Grignard reagent derived from bromide **15** to aldehyde **7**.[8] Bromide **15** in turn was prepared as a 9:1 *E:Z* mixture of isomers with the required *E*-stereochemistry being introduced *via* a stereoselective Julia ring opening of a cyclopropane (Scheme 3). This latter approach gave higher selectivity for the *E*-olefin than an earlier synthesis of bromide **15** based on a carbonyl ene reaction.[14]

In the present work bromide **15** was prepared *via* modification of the reported synthesis of 5-bromo-2,3-dimethyl-2-pentene.[15] Alkylation of the carbanion generated from 2-acetylbutyrolactone **16** with ethyl iodide followed by chloride assisted decarboxylation of the alkylated product **17** afforded chloropentanone **18** in high yield. Subsequent treatment of chloropentanone **18** with sodium hydroxide then resulted in formation of cyclopropane **19** in 73% yield. Reduction of the ketone **19** with lithium aluminium hydride afforded alcohol **20** in 74% yield which upon conversion to the corresponding bromide using lithium bromide and phosphorus tribromide allowed stereoselective formation of the desired (*E*)-alkene **15** in 61% yield as a 9:1 *E:Z* mixture upon treatment with zinc bromide. This approach to (*E*)-alkene **15** not only proceeded with better stereoselectivity than our earlier approach utilizing a carbonyl-ene reaction but was also more amenable to large scale synthesis.

With bromide **15** in hand, generation of the Grignard reagent followed by addition to aldehyde **7** proceeded as reported earlier[8] providing alcohol **9** in moderate yield. Epoxidation of the acetate derivative **10** with *m*-chloroperoxybenzoic acid and dimethyldioxirane afforded a 1:1 mixture of epoxides **28** and **31**. Based

on the lasalocid work cited above, metal assisted epoxidation of alcohol **9** would have led to preferential formation of the undesired epoxide **30** thus aternative epoxidation methods were sought.

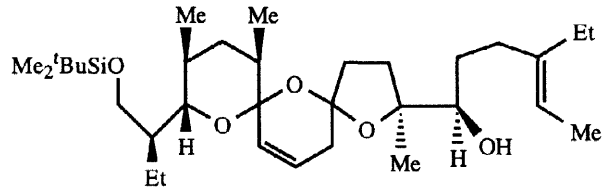


16 **17** **18** **19** **20** **15**

Reagents and conditions: (a) Na, MeOH, benzene, ethyl iodide, reflux; yield 82%. (b) 14.5% aq. HCl; yield 92%. (c) NaOH, reflux; yield 73%; (d) $LiAlH_4$; yield 74%. (e) LiBr, PBr_3, collidine then $ZnBr_2$, Et_2O; yield 61%.

Scheme 3.

It was envisaged that using the appropriate chiral ligand, Sharpless asymmetric dihydroxylation[16] of alkene **35** could be directed from the β-face. This approach relies on the powerful facial selectivity of the chiral ligand overriding any inherent facial selectivity in the olefin. The ligand facial selectivity would manifest itself as a diastereomeric excess in the asymmetric dihydroxylation of olefin **35** in the natural product synthesis, whereas in the model work described herein, the ligand facial selectivity would be measured by the enantiomeric excess of the diastereomeric diols **22** [or **23**] and **25** [or **26**] formed.

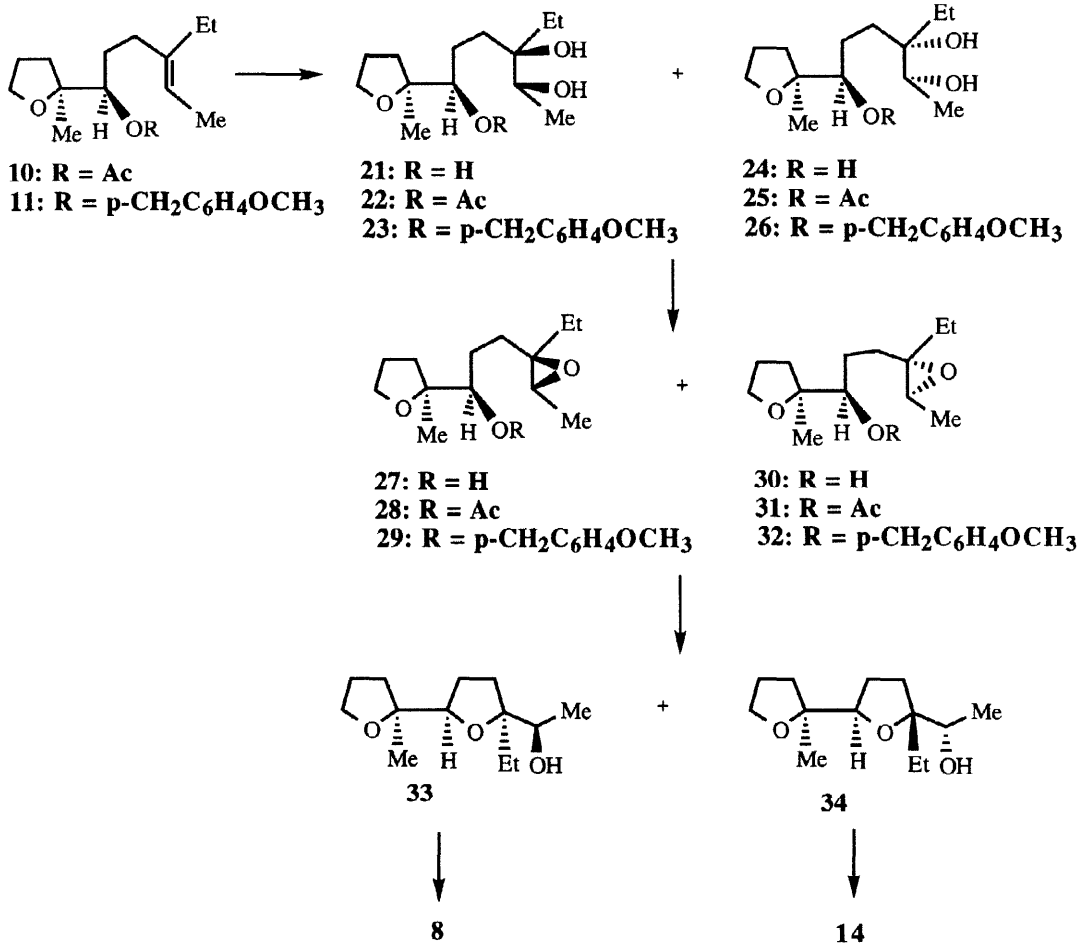


35

With these thoughts in mind, acetate **10** was treated with osmium tetroxide (0.01 equiv.), $(DHQD)_2$-PHAL (0.05 equiv.), potassium ferricyanide and methanesulfonamide in *tert*-butanol providing the diols **22** and **25** as a 1:1 inseparable mixture of diastereomers in 73% yield (Scheme 4). It was then necessary to establish the methodology for conversion of diols **22** and **25** to epoxides **28** and **31** with retention of stereochemistry. Using the protocol established for this transformation by Sharpless *et al.*,[17] diols **22** and **25** were treated sequentially with trimethyl orthoacetate, acetyl bromide and potassium carbonate in an attempt to prepare epoxides **28** and **31**, however, only a complex mixture resulted.

Given that the acetate group in diols **22** and **25** may have complicated the hydrolysis of the haloacetate intermediate in the attempted conversion of the diol to an epoxide, use of a *p*-methoxybenzyl group as an alternative protecting group for the secondary alcohol was investigated. Thus, subjection of ether **11** to Sharpless asymmetric dihydroxylation as described above for acetate **10** provided the diols **23** and **26** in a 1:1 ratio and in 92% yield. In this case attempted conversion to epoxides **29** and **32** as described above was also

unsuccessful. Upon examination of the literature it then became evident that transformation of a diol to an epoxide with retention of stereochemistry has not been demonstrated using a 1,2-diol derived from a trisubstituted alkene.



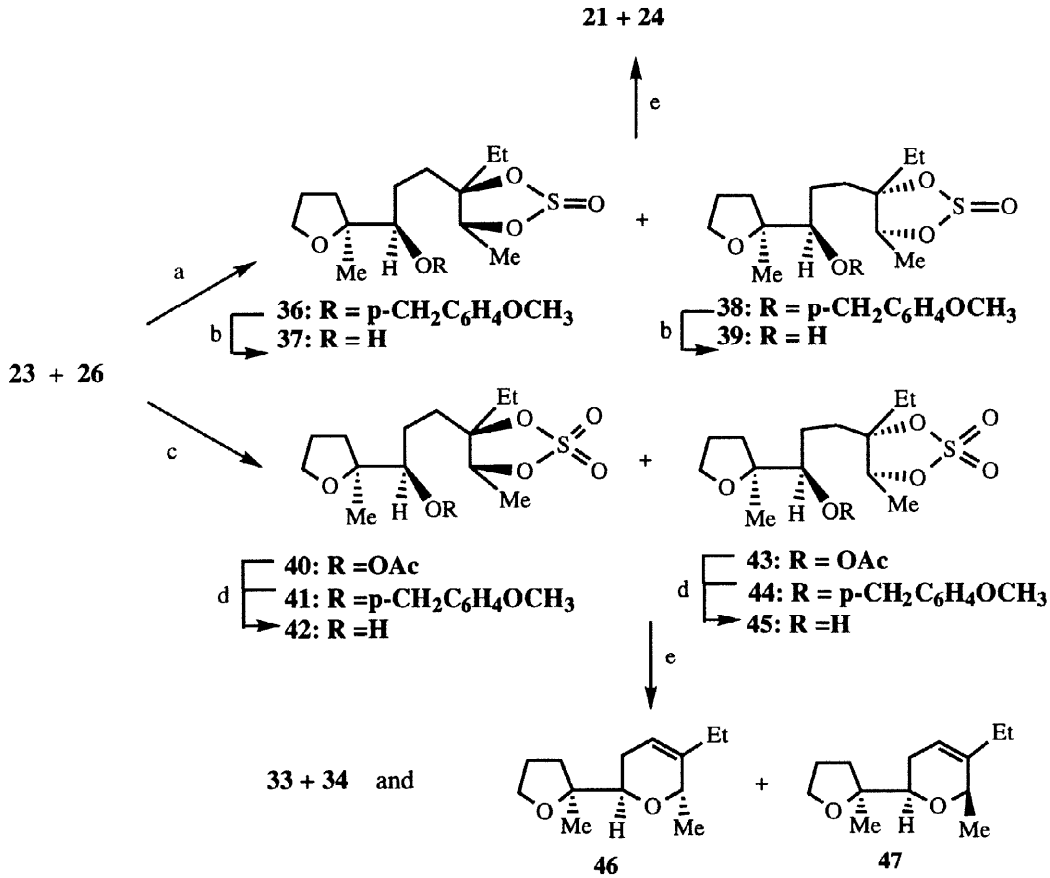
Scheme 4

Given the inability to convert diols **22** and **23** [and **25** or **26** respectively] to epoxides **28** and **29** [and **31** or **32** respectively], we next turned our attention to the use of a cyclic sulfate[18] as an alternative to an epoxide in the key cyclization reaction (Scheme 5).

Treatment of diols **22**, **23** [and **25** or **26** respectively] with thionyl chloride and triethylamine followed by oxidation with ruthenium(III) trichloride and sodium periodate afforded cyclic sulfates **40** and **41** [and **43** or **44** respectively]. Acid catalyzed cyclisation of a hydroxyl group liberated *in situ* from hydrolysis of a protected alcohol onto a cyclic sulfate has been reported.[19] In our case attempts to effect this transformation by treatment of cyclic sulfates **40** and **41** [and **43** or **44** respectively] with 5% H_2SO_4 in acetonitrile under reflux for 20 h afforded only recovered starting material. It was therefore hoped that acid catalyzed cyclization of the corresponding alcohols **42** and **45** would be more fruitful.

Treatment of *p*-methoxybenzyl ethers **41** and **44** with DDQ in wet dichloromethane afforded alcohols **42** and **45** in good yield, however attempts to effect cyclization of the alcohol onto the sulfate upon refluxing in

aqueous acetonitrile were unsuccessful. At this stage cyclization under basic conditions was investigated. Treatment of **42** and **45** with excess sodium hydride in DMF resulted in no reaction, however use of sodium hydride in ethanol followed by hydrolysis of the resultant alkyl sulfate afforded a 1:1 mixture of tetrahydrofurans **33** and **34** in 18% yield together with a 1:1 mixture of tetrahydropyrans **46** and **47** in 28% yield. Thus, the endo mode of cyclization was favoured moderately over the exo mode of cyclization, however, the acidic conditions required to effect hydrolysis of the initial alkyl sulfate product also effected undesired elimination to the alkenes **46** and **47**.



Reagents and conditions: (a) $SOCl_2$, Et_3N, Et_2O, 0°C; yield 88%. (b) DDQ, H_2O, CH_2Cl_2; yield 95%. (c) $SOCl_2$, Et_3N, Et_2O, 0°C then $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN; yield 60%; (d) DDQ, H_2O, CH_2Cl_2; yield 74%. (e) NaH, EtOH, room temp.; yield 66%. (f) NaH, EtOH, room temp., then Et_2O, 20% H_2SO_4; yield **33** and **34** 18% **46** and **47** 28%.

Scheme 5

In order to avoid the acidic conditions needed to hydrolyse an alkyl sulfate to an alcohol, use of cyclic sulfites **37** and **39** as a cyclization precursor was also investigated. In this case cyclization under basic conditions would be followed directly by loss of sulfur dioxide without the need for a hydrolysis step. Unfortunately, treatment of sulfites **37** and **39** with sodium hydride in ethanol or potassium hydride and 18-crown-6 in DMF only afforded triols **21** and **24** presumably due to steric hindrance in the cyclization step and

the use of a less electrophilic cyclization precursor. Cyclizations of hydroxyl groups onto cyclic sulfites and sulfates reported in the literature have been restricted to examples using cyclic sulfites and sulfates derived from disubstituted alkenes.

In order to demonstrate the feasibilty of the epoxidation/cyclization strategy (Scheme 4) olefin **10** was treated with dimethyldioxirane in acetone affording a 1:1 mixture of epoxides **28** and **31** in 81% yield. Deprotection of the acetate group using potassium carbonate in methanol afforded alcohols **27** and **30** which then underwent smooth cyclization using a catalytic quantity of camphorsulfonic acid in dichloromethane to the tetrahydrofurans **33** and **34** in 96% yield which were readily separated by flash chromatography. Finally mesylation followed by silver assisted ring expansion using silver carbonate afforded the tetrahydropyrans **8** and **14** from **33** and **34** respectively.

In summary, the successful conversion of olefin **10** to the tetrahydropyrans **8** and **14** *via* epoxides **27** and **30** demonstrates a method for constructing the E-ring of *epi*-deoxy-O-8-salinomycin from alkene **35**. Attempts to provide a stereoselective method for formation of the epoxide **27** required for cyclization to the correct tetrahydrofuran **33**, and hence the correct tetrahydropyran **8**, utilizing Sharpless asymmetric dihydroxylation were, however, unsuccessful.

EXPERIMENTAL

General Details:- Melting points were determined using a Reichert Kofler block and are uncorrected. Infrared absorption spectra were recorded using Perkin Elmer 1600 Series FTIR spectrometer as Nujol Mulls or thin films between sodium chloride plates. ^{1}H NMR spectra were obtained using either a Bruker AM 400 or Bruker AC 200 spectrometer. ^{13}C NMR data were recorded using a Bruker AM 400 or Bruker AC 200 spectrometer. ^{13}C NMR spectra were interpreted with the aid of DEPT 135 and DEPT 90 experiments. Low resolution mass spectra were recorded using a VG 70-SE spectrometer operating at an accelerating voltage of 70 eV. High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Elemental analyses were performed at the Microanalytical Laboratory, University of New South Wales, Sydney. Flash chromatography was performed using Merck Kieselgel 60 (230-400 Mesh) with the indicated solvents.

2-Acetyl-2-ethyl-γ-butyrolactone 17. The title compound was prepared using a modification of the procedure reported by Ward et al.[15] 2-Acetyl-γ-butyrolactone **16** (27.7 g, 216 mmol) in anhydrous benzene (200 mL) was added dropwise to a stirred suspension of sodium metal (8 g, 348 mmol) in benzene (300 mL) containing methanol (1.5 mL) under nitrogen. The reaction mixture became cloudy upon addition of the lactone. The reaction mixture was stirred overnight, then heated under reflux for 3 h under nitrogen. While the reaction mixture was still warm, ethyl iodide (126.7 g, 802 mmol) was added and the reaction heated under reflux for 4 h after which it was left stirring overnight at room temperature. Sodium iodide was removed by filtration and washed several times with ethyl acetate. Evaporation of the combined filtrates afforded a pale yellow oil which was purified by distillation under reduced pressure to afford the product **17** (39.2 g, 82%) as a colourless oil, b.p. 127-130 °C/16 mm Hg (lit.[20] 127 °C/16-18 mm Hg).

5-Chloro-3-ethyl-2-pentanone 18. 2-Acetyl-2-ethyl-γ-butyrolactone **17** (39.2 g, 252 mmol) was added with stirring to a solution of hydrochloric acid (43 mL of a 32% solution, 379 mmol) and distilled water (51 mL) and the resultant mixture carefully heated until all gas evolution had ceased. The reaction mixture was distilled and 75 mL of distillate collected after which water (50 mL) was added and a further 60 mL of distillate collected. The aqueous layer was separated and extracted with ether (3 x 100 mL). The combined organic layers were dried over calcium chloride and the solvent evaporated to give the title compound **18** (34.4 g, 92%) as a pale yellow oil which was used without further purification. Spectroscopic data for this product were in agreement to the data reported in the literature.[20]

1-Acetyl-1-ethylcyclopropane 19. Chloride **18** (34.4 g, 232 mmol) was slowly added to a stirred solution of sodium hydroxide (14.3 g, 358 mmol) in water (18 mL). The mixture was then heated under reflux for 2 h, water (33 mL) was added and the reaction mixture heated for an additional 1.5 h. The water / ketone mixture was distilled until all the organic layer was removed from the reaction mixture. The organic layer of the distillate was separated and the aqueous layer saturated with solid potassium carbonate. The aqueous layer was extracted with ether and the combined organic layers dried over magnesium sulfate and then fractionally distilled to afford the title compound **19** (19 g, 73%) as a colourless liquid which was sufficiently pure for use in the next step, b.p. 145.5-148 °C/760 mm Hg (lit. [20] 145-148 °C/760 mm Hg).

1-(1'-Ethylcyclopropyl)ethanol 20. A solution of ketone **19** (8 g, 71.4 mmol) in anhydrous ether (80 mL) was added dropwise to a stirred mixture of lithium aluminium hydride (27 mL of a 1M solution in ether, 27 mmol) in anhydrous ether (280 mL) at 0 °C under nitrogen. The reaction mixture was stirred at this temperature for 2 h, quenched with saturated sodium sulphate (8 mL), then warmed to room temperature. The precipitate was filtered and washed several times with ether. The combined ether extracts were dried over sodium sulphate and the solvent removed under reduced pressure to afford a colourless oil. Purification of the crude material by flash chromatography using pentane/ether (4:1) as eluent afforded the title compound **20** (6 g, 74%) as a clear oil; IR (neat): ν (cm^{-1}) 3371 (b, OH), 2968 (s), 1455 (s), 1373 (s), 1290 (b), 1102 (s), 1078 (s); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.30-0.40 (4H, m, CH_2) 0.87 (3H, t, $J_{2'',1''}$ 7.4 Hz, $CH_2\underline{CH_3}$), 1.16 (3H, d, $J_{2,1}$ 6.5 Hz, CH_3), 1.32 (1H, m, OH), 1.58 (2H, q, $J_{1'',2''}$ 7.4 Hz, $\underline{CH_2}CH_3$), 3.39 (1H, q, $J_{1,2}$ 6.5 Hz, C<u>H</u>OH); ^{13}C NMR (50 MHz; $CDCl_3$): δ 8.2, 9.2 (2 x CH_2, C-2', C-3'), 10.7 (CH_3, C-2''), 19.4 (CH_3, C-2), 24.7 (CH_2, C-1''), 25.8 (quat., C-1'), 72.5 (CH, C-1'); MS (CI, CH_4): *m/z* (%) 113 (M-H, 100) and 85 (M-C_2H_5, 21).

(E)-1-Bromo-3-ethyl-3-pentene 15. Lithium bromide (5 g, 57.6 mmol) was added to a mixture of alcohol **20** (2 g, 17.5 mmol) and collidine (2.5 mL, 17.7 mmol) in anhydrous ether (52 mL) cooled to -30 °C. The resultant suspension was cooled to -50 °C and stirred vigorously while phosphorous tribromide (1.67 mL, 17.58 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to 0 °C over 1 h and stirred at this temperature for a further 6 h. Collidine (3.3 mL, 23.9 mmol) was added, followed by water (10 mL) and the aqueous layer extracted with ether (4 x 15 mL). The combined organic layers were washed sequentially with saturated sodium bicarbonate (10 mL), brine (10 mL) and dried over sodium sulphate. Removal of the solvent under reduced pressure afford a colourless oil which was diluted with anhydrous ether (3.3 mL) and added dropwise with stirring to a cooled (-40 °C) suspension of zinc bromide (4 g, 17.76 mmol)

in anhydrous ether (6.8 mL). Ether (3.3 mL) was used to transfer any remaining bromide into the reaction mixture. The resultant suspension was allowed to warm to 0 °C over 1 h and stirring continued for a further 4 h, then brine (5 mL) and ether (1 mL) were added. The organic layer was separated and the aqueous layer extracted with pentane (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulphate. Evaporation of the solvent under reduced pressure afforded a colourless oil which was purified by flash chromatography using pentane as the eluent to give the title compound **15** (1.49 g, 61%) as a clear oil and as a 9:1 mixture of *E/Z* isomers. ^{1}H NMR, ^{13}C NMR and mass spectrometry data were in agreement to those reported in the literature.[14]

(4E, 1R*, 2'S*)-4-Ethyl-1-(4''-methoxybenzyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene 11. Sodium hydride (213 mg, 60% dispersion in oil, 5.32 mmol) was added to a solution of alcohol **9**[8] (366 mg, 1.74 mmol) in anhydrous DMF (2 ml) and the reaction mixture stirred for 1 h at room temperature. 4-Methoxybenzyl chloride (277 mg, 1.77 mmol) and tetrabutyl ammonium iodide (5 mg) were added to the reaction mixture and stirring continued for 48 h. Ethanol (1 ml) followed by water (0.5 ml) were added to quench the excess sodium hydride and the resultant aqueous layer was extracted with ethyl acetate (3 x 7 ml). The organic layers were combined, washed with water (5 ml), dried (sodium sulphate) and the solvent removed under reduced pressure to afford an orange oil which was purified by flash chromatography using hexane / ethyl acetate (9:1) as eluent to afford the *title compound* **11** as a colourless oil (500 mg, 87%); IR (neat): ν (cm^{-1}) 2967 (s), 2869 (s), 1610 (s), 1512 (s), 1463 (m), 1448 (m), 1247 (s, C-O-C asym), 1097, 1041 (b, C-O-C sym); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (3H, t, $J_{2'',1''}$ 7.6 Hz, $CH_2\underline{CH_3}$), 1.15 (3H, s, 2'-Me), 1.38-2.35 (10H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.7 Hz, H-6), 3.32 (1H, dd, $J_{1,2A}$ 9.5, $J_{1,2B}$ 2.6 Hz, H-1), 3.71-3.87 (2H, m, CH_2O), 3.80 (3H, s, OMe), 4.53 (1H, d, $J_{HA,HB}$ 11.7 Hz, $C\underline{H}_AH_BAr$), 4.74 (1H, d, $J_{HB,HA}$ 11.7 Hz, $CH_A\underline{H}_BAr$), 5.15 (1H, q, $J_{5,6}$ 6.6 Hz, H-5), 7.22 (2H, d, *J* 8.4 Hz, Ar-H), 7.45 (2H, d, *J* 8.4 Hz, Ar-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ 12.7 (CH_3, C-2''), 12.8 (CH_3, C-6), 22.6 (CH_3, 2'-Me), 23.8 (CH_2), 26.4 (CH_2), 30.5 (CH_2), 32.9 (CH_2), 33.4 (CH_2), 55.0 (OCH_3), 67.7 (CH_2, C-5'), 74.2 (CH_2, OCH_2Ar), 84.4 (CH, C-1), 86.1 (quat., C-2'), 113.5 (CH, C-3'''), 117.8 (CH, C-5), 129.2 (CH, C-2'''), 141.5 (quat., C-1'''), 158.9 (quat., C-4'''); MS (CI, CH_4): *m/z* (%) 333 (M+H, 14) 121 (M-$C_{13}H_{23}O_2$, 100) and 85 (M-$C_{16}H_{23}O_2$, 16); HRMS: calculated for $C_{21}H_{33}O_3$ $(M+H)^+$, 333.24292, found 333.24297.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-1,4,5-hexanetriol 21 and 24. Sodium hydride (7 mg, 0.3 mmol) was cooled to 0 °C and ethanol (3.5 mL) added. A solution of cyclic sulfite **37** (and **39**) (63 mg, 0.2 mmol) in ethanol (3 mL) was cooled to 0 °C and added dropwise to the sodium ethoxide solution. The resultant suspension was stirred overnight, allowing the reaction to warm to room temperature. Ethanol was removed under reduced pressure to afford a colourless oil which was purified by flash chromatography using hexane/ethyl acetate (1:1) and then (1:2) as eluent to afford the *title compounds* **21** and **24** (50 mg, 94%) as a colourless oil; IR (neat): ν (cm^{-1}) 3401 (b, OH), 2970 (s), and 1235 (C-O-C asym); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.83, 0.88* (3H, t, $J_{2'',1''}$ 7.0 Hz, $CH_2C\underline{H_3}$), 1.09, 1.10* (3H, s, 2'-Me), 1.15-2.10 (13H, m, CH_2, H-6) 2.50 (1H, s, OH), 3.46 (1H, dd, $J_{1,2A}$ 10.3, $J_{1,2B}$ 2.0 Hz, H-1) 3.66 (1H, q, $J_{5,6}$ 6.8 Hz, H-5), 3.63-3.91 (3H, m, CH_2O and OH), 4.25 (1H, s, OH); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.5, 7.8* (CH_3, C-2''), 17.0 (CH_3, C-6), 22.7, 22.9* (CH_3, 2'-Me), 25.1, 25.1* (CH_2), 26.1, 26.3* (CH_2), 26.9 (CH_2), 31.0, 31.1* (CH_2), 32.2 (CH_2), 67.9 (CH_2, C-5'), 70.8, 71.7* (CH, C-5), 75.7, 75.9* (quat.,

C-4), 77.1, 77.3* (CH, C-1), 85.7, 85.8* (quat., C-2'); MS (CI, CH_4): *m/z* (%) 247 (M-H, 12), 229 (M-OH, 50), 211 (100), and 85 (M-$C_8H_{17}O_3$, 12); HRMS: calculated for $C_{13}H_{27}O_4$ $(M+H)^+$, 247.1909, found 247.1882.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-,4,5-dihydroxyhex-1-yl acetate 22 and 25. A solution of K_2CO_3 (147 mg, 1.06 mmol, 3 equiv.), $K_3Fe(CN)_6$ (350 mg, 1.06 mmol, 3 equiv.), $MeSO_2NH_2$ (34 mg, 0.35 mmol, 1 equiv.), $K_2OsO_4.2H_2O$ (1 mg, 0.01 equiv.) and $(DHQD)_2PHAL$ (14 mg, 0.05 equiv.) in *tert*-butyl alcohol-water 1:1 (3.5 ml) was cooled to 0 °C. The resulting suspension was treated with acetate **10** (90 mg, 0.35 mmol, 1 equiv.) and the mixture stirred at this temperature until no starting material was evident by tlc (approximately 36 h). The reaction was quenched using $Na_2S_2O_5$ (790 mg, 5 mmol) and warmed to room temperature after which ethyl acetate (2 ml) was added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 7 ml). The organic layers were combined, dried over magnesium sulphate and the solvent removed under reduced pressure to give a residue which was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluent to afford a mixture of **22** and **25** as a colourless oil (75 mg, 73%); IR (neat): ν (cm^{-1}) 3448 (b, OH), 2966 (s), 2872 (s), 1731 (s, C=O) and 1235 (b, C-O-C asym); ^1H NMR (200 MHz; $CDCl_3$): δ 0.86, 0.88* (3H, t, $J_{2'',1''}$ 7.5 Hz, $CH_2\underline{CH_3}$), 1.14, 1.15* (3H, d, $J_{6,5}$ 6.8 Hz, H-6), 1.18 (3H, s, 2'-Me), 1.35-2.10 (10H, m, CH_2), 2.08 (3H, s, CH_3CO), 3.10 (1H, s, OH), 3.47 (1H, q, $J_{5,6}$ 6.8 Hz, H-5), 3.64-3.92 (3H, m, CH_2O and OH), 4.87 (1H, d, $J_{1,2}$ 9.0 Hz, CHOAc); ^{13}C NMR (50 MHz; $CDCl_3$): δ 8.2, 8.4* (CH_3, C-2''), 18.0 (CH_3, C-6), 21.4 (CH_3, CH_3CO), 23.1 (CH_3, 2'-Me), 25.1, 25.2* (CH_2), 27.0 (CH_2), 28.0, 28.1* (CH_2), 32.5, 32.6* (CH_2), 35.6 (CH_2), 69.0 (CH_2, C-5'), 71.8, 71.9* (CH, C-5), 76.0 (quat., C-4), 79.3, 79.4* (CH, C-1), 84.7 (quat., C-2'), 171.1 (quat., C=O); MS (CI, CH_4): *m/z* (%) 288 (M^+, 6), 271 (M-OH, 7), 211 (M-$C_2H_5O_3$, 100), 193 (M-$C_2H_7O_4$, 61), and 85 (M-$C_{10}H_{19}O_4$, 14); HRMS: calculated for $C_{15}H_{29}O_5$ $(M+H)^+$, 289.2015, found 289.1977.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-(4''-methoxybenzyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4,5-hexanediol 23 and 26. K_2CO_3 (325 mg, 2.35 mmol, 3 equiv.), $K_3Fe(CN)_6$ (773 mg, 2.35 mmol, 3 equiv.), $MeSO_2NH_2$ (75 mg, 0.79 mmol, 1 equiv.), $K_2OsO_4.2H_2O$ (3 mg, 0.01 equiv.) and $(DHQD)_2PHAL$ (63 mg, 0.08 mmol, 0.1 equiv.) were dissolved in a 1:1 mixture of *tert*-butyl alcohol and water (7.6 ml) and cooled to 0 °C. The resulting suspension was treated with ether **11** (268 mg, 0.74 mmol, 1 equiv.) and the mixture stirred at this temperature until no starting material was evident by tlc (approximately 120 h). The reaction was quenched using $Na_2S_2O_5$ (790 mg, 5 mmol) and warmed to room temperature after which ethyl acetate (7.5 ml) was added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 10 ml). The organic layers were combined, washed with 2M KOH (7.5 ml, 15 mmol), dried over magnesium sulphate and the solvent removed under reduced pressure to afford a residue which was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluent to give a mixture of **23** and **26** as a colourless oil (272 mg, 92%); IR (neat): ν (cm^{-1}) 3436 (b, OH), 2966 (m), 2872 (m), 1707 (m), 1613 (s), 1514 (s), 1455 (m) and 1243 (b, C-O-C asym); ^1H NMR (200 MHz; $CDCl_3$): δ 0.85 (3H, t, $J_{2'',1''}$ 7.3 Hz, $CH_2C\underline{H_3}$), 1.10 (3H, d, $J_{6,5}$ 6.3 Hz, H-6), 1.16 (3H, s, 2'-Me), 1.34-2.10 (10H, m, CH_2), 3.29 (1H, d, $J_{1,2}$ 7.0 Hz, H-1), 3.64 (1H, q, $J_{5,6}$ 6.3 Hz, H-5), 3.70-3.95 (2H, m, CH_2O), 3.75 (3H, s, OMe), 4.53 (1H, d, $J_{HA,HB}$ 11 Hz, $C\underline{H_A}CH_BAr$), 4.53 (1H, d, $J_{HB,HA}$ 11 Hz, $CH_AC\underline{H_B}Ar$), 6.85 (2H, d, *J* 8.3 Hz, Ar-H), 7.26 (2H, d, *J* 8.3 Hz, Ar-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.2, 7.4* (CH_3, C-2''), 16.5, 16.7* (CH_3, C-6), 23.3, 23.3* (CH_3, 2'-Me), 24.9 (CH_2), 26.0 (CH_2), 31.5, 31.6* (CH_2), 33.0 (CH_2), 34.7 (CH_2), 54.7 (CH_3, OMe), 67.4 (CH_2, C-5'),

70.8, 70.9* (CH, C-5), 73.5, 73.9* (quat., C-4), 75.6 (CH_2, CH_2Ar), 84.8, 84.9* (CH, C-1), 85.9, 86.0* (quat., C-2'), 113.3 (CH, C-3'''), 129.2, 129.3* (CH, C-2'''), 130.7 (quat., C-1'''), 158.7 (quat., C-4'''); MS (CI, CH_4): *m/z* (%) 367 (M+H, 14), 121 (M- $C_{13}H_{11}O_3$, 18), 121 (M-$C_{13}H_{25}O_4$, 100) and 85 (M-$C_{16}H_{25}O_4$, 6); HRMS: calculated for $C_{21}H_{35}O_5$ $(M+H)^+$, 367.2484, found 367.2484.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4,5-Epoxy-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-1-hexanol 27 and 30. To a solution of acetate (**28** and **31**) (147 mg, 0.6 mmol) in 95% methanol (5 mL) was added potassium carbonate (327 mg, 2.2 mmol). After stirring for 16 h, a saturated solution of sodium chloride (5 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 10 mL).The organic layers were combined, dried over magnesium sulphate and the solvent removed under reduced pressure to afford a residue which was purified by flash chromatography, using hexane/ethyl acetate (4:1) as eluent to give a mixture of epoxides **27** and **30** as a colourless oil (272 mg, 92%); IR (neat): ν (cm^{-1}) 3467 (b, OH), 2968 (s), 2872 (s), 1462, 1378 (s), 1301 (C-O-C asym), 1077, 1045 (C-O-C sym), 967 (epoxide) and 878 (epoxide); ^1H NMR (200 MHz; $CDCl_3$): δ 0.89 (3H, t, $J_{2'',1''}$ 7.4 Hz, $CH_2\underline{CH_3}$), 1.13 (3H, s, 2'-Me), 1.05, 1.06* (3H, d, $J_{6,5}$ 6.5 Hz, H-6), 1.39-2.18 (10H, m, CH_2), 3.45 (1H, m, H-1), 3.72-3.99 (3H, m, CH_2O, H-5); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.8 (CH_3, C-2''), 17.1, 17.5* (CH_3, C-6), 23.4 (CH_3, Me-2'), 25.0 (CH_2), 25.9, 26.4* (CH_2), 27.7, 28.2* (CH_2), 29.3, 30.1* (CH_2), 32.6, 34.4* (CH_2), 68.0, 68.4* (CH_2, C-5'), 69.1 (quat., C-4), 72.3 (CH, C-5), 84.1, 84.3* (quat., C-2'), 85.1, 86.7* (CH, C-1); Reacetylation of a sample of **27** and **30** afforded acetates **28** and **31**: HRMS: calculated for $C_{15}H_{27}O_4$ $(M+H)^+$, 271.1909, found 271.1921.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4,5-Epoxy-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)hex-1-yl acetate 28 and 31. Freshly prepared dimethyl dioxirane (8 ml) was added to a solution of acetate **10** (162 mg, 0.64 mmol) in acetone (6 ml) under an atmosphere of nitrogen. The reaction was stirred for 36 h at room temperature however the presence of the starting acetate **10** was still evident by tlc. The solvent was removed under reduced pressure to afford a colourless oil which was dried over magnesium sulfate and purified by flash chromatography using hexane/ethyl acetate (9:1) as eluent to afford epoxide **28** (140 mg, 81%) as a clear oil; IR (neat): ν (cm^{-1}) 2966 (s), 2872 (s), 1736 (s, C=O), 1455 (b), 1373 (s), 1232 (b, C-O-C asym), 1038 (b, C-O-C sym), 967 (epoxide) and 885 (epoxide); ^1H NMR (200 MHz; $CDCl_3$): δ 0.95 (3H, t, $J_{2'',1''}$ 7.5 Hz, $CH_2\underline{CH_3}$), 1.16 (3H, s, 2'-Me), 1.26 (3H, d, $J_{6,5}$ 5.3 Hz, H-6), 1.35-2.30 (10H, m, CH_2), 2.05 (3H, s, CH_3CO), 2.85 (1H, q, $J_{5,6}$ 5.3 Hz, H-5), 3.71-3.91 (2H, m, CH_2O), 4.85(1H, d, $J_{1,2}$ 7.7 Hz, H-1); ^{13}C NMR (50 MHz; $CDCl_3$): δ 9.2, 9.3* (CH_3, C-2''), 13.5 (CH_3, C-6), 20.9 (CH_3, CH_3CO), 22.2, 22.4* (CH_3, Me-2'), 22.7, 22.9* (CH_2), 24.5 (CH_2), 25.7 (CH_2), 30.7, 30.8* (CH_2), 34.4 (CH_2), 58.9, 59.0* (CH, C-5), 63.3, 63.6* (quat., C-4), 68.2 (CH_2, C-5'), 77.3, 77.5* (CH, C-1), 83.5 (quat., C-2'), 170.7 (quat., C=O); MS (CI, CH_4): *m/z* (%) 284 (M+CH_3, 34), 269 (M-H, 26), 225 (50), 211 (M-$C_2H_3O_2$, 100), 193 (M-$C_2H_5O_3$, 69) and 85 (M-$C_{10}H_{17}O_3$, 45); HRMS: calculated for $C_{15}H_{27}O_4$ $(M+H)^+$, 271.1909, found 271.1927.

(2S*, 5R*, 1'R, 2"S*)- and (2R*, 5R*, 1'S, 2"S*)-2-Ethyl-2-(1-hydroxyethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran 33 and 34.

To a solution of epoxides (**27** and **30**) (105 mg, 0.5 mmol) in dichloromethane (1.5 mL) was added camphorsulfonic acid (5 mg). After stirring for 16 h, the solvent was removed under reduced pressure to

afford a residue which was purified by flash chromatography, using hexane/ethyl acetate (3:2) as eluent to afford:

(i). *bistetrahydrofuran* **33** as a colourless oil (55 mg, 52%); IR (neat): ν (cm^{-1}) 3445 (b, OH), 2962 (s), 2866 (s), 1450 (s), 1369 (s), 1114 (s), 1232 (b, C-O-C asym), 1074 (s, C-O-C sym), 1050 (s, C-O-C sym); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.88 (3H, t, $J_{2''',1'''}$ 7.7 Hz, $CH_2C\underline{H}_3$), 1.05 (3H, d, $J_{2',1'}$ 6.6 Hz, 1'-Me), 1.11 (3H, s, 2''-Me), 1.40-2.15 (10H, m, CH_2), 2.44 (1H, s, OH), 3.84 (2H, t, $J_{5'',4''}$ 6.4 Hz, CH_2O), 3.93 (1H, q, $J_{1',2'}$ 6.6 Hz, C<u>H</u>OH), 3.97 (1H, dd, $J_{5,4A}$ 10.6, $J_{5,4B}$ 5.1 Hz, H-5); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.6 (CH_3, C-2'''), 17.1, (CH_3, 2'-Me), 23.3 (CH_3, C-2'), 26.3 (CH_2), 28.1 (CH_2), 29.3 (CH_2), 29.9 (CH_2), 32.7 (CH_2), 68.0 (CH_2, C-5''), 69.1 (CH, C-1'), 84.1 (quat., C-2), 86.7 (CH, C-5) 88.4 (quat., C-2''); MS (CI, CH_4): *m/z* (%) 229 (M+H, 19), 212 (M-O, 23), 183 (M-C_2H_5O, 38), 111 (M-$C_6H_{13}O_2$, 36) and 85 (M-$C_8H_{15}O_2$, 100); HRMS: calculated for $C_{13}H_{24}O_3$ $(M+H)^+$, 229.1804, found 229.1806.

(ii). *bistetrahydrofuran* **34** as a colourless oil (46 mg, 44%); IR (neat): ν (cm^{-1}) 3445 (b, OH), 2962 (s), 2866 (s), 1450 (s), 1369 (s), 1114 (s), 1232 (b, C-O-C asym), 1074 (s, C-O-C sym), 1050 (s, C-O-C sym); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.88 (3H, t, $J_{2''',1'''}$ 7.4 Hz, $CH_2C\underline{H}_3$), 1.03 (3H, d, $J_{2',1'}$ 6.6 Hz, 1'-Me), 1.26 (3H, s, 2''-Me), 1.41 (2H, q, $J_{2''',1'''}$ 7.4 Hz, $C\underline{H}_2CH_3$), 1.40-2.15 (9H, m, CH_2, OH), 3.71-3.96 (4H, m, CH_2O, C<u>H</u>OH, H-5); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.7 (CH_3, C-2'''), 17.4, (CH_3, 2'-Me), 24.9 (CH_3, C-2'), 25.8 (CH_2), 27.6 (CH_2), 28.1 (CH_2), 30.1 (CH_2), 34.4 (CH_2), 68.3 (CH_2, C-5''), 72.3 (CH, C-1'), 84.3 (quat., C-2), 85.1 (CH, C-5), 89.3 (quat., C-2''); MS (CI, CH_4): *m/z* (%) 229 (M+H, 19), 212 (M-O, 23), 183 (M-C_2H_5O, 38), 111 (M-$C_6H_{13}O_2$, 36) and 85 (M-$C_8H_{15}O_2$, 100); HRMS: calculated for $C_{13}H_{25}O_3$ $(M+H)^+$, 229.1804, found 229.1806.

(2S*, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 8. To a solution of bistetrahydrofuran **33** (25 mg, 0.1 mmol) in dichloromethane (0.3 mL) was added pyridine (0.5 mL). The reaction mixture was cooled to 0 °C and methanesulfonyl chloride (13 μL, 0.2 mmol) was added and stirring continued for 16 h allowing the reaction to warm to room temperature. The volatile components were removed under reduced pressure, the crude mesylate dissolved in acetone (0.5 ml) and silver carbonate (12.7 mg, 46 μmol) and distilled water (5 drops) were added. After stirring for 48 h. the reaction mixture was filtered through glass wool and washed with ethyl acetate (10 ml). The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to afford a residue which was purified by flash chromatography, using hexane/ethyl acetate (3:2) as eluent to afford the *title compound* **8** (17 mg, 68%) as a colourless oil. ^{1}H NMR, ^{13}C NMR and mass spectrometry data were in agreement with that reported in the literature.[8]

(2R*, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran 14. To a solution of bistetrahydrofuran **34** (16 mg, 0.07 mmol) in dichloromethane (0.3 mL) was added pyridine (0.4 mL). The reaction mixture was cooled to 0 °C and methanesulfonyl chloride (8 μL, 0.1 mmol) was added and stirring continued for 16 h allowing the reaction to warm to room temperature. Volatiles were removed under reduced pressure and the crude mesylate dissolved in acetone (0.4 ml) and silver carbonate (12.7 mg, 46 μmol) and distilled water (5 drops) were added. After stirring for 48 h. the reaction mixture was filtered through glass wool and washed with ethyl acetate (10 ml). The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to afford a residue which was purified by flash chromatography, using hexane/ethyl acetate (3:2) as eluent, to afford the *title compound* **14**

(10 mg, 63%) as a colourless oil. ^{1}H NMR, ^{13}C NMR and mass spectrometry data for this product were in agreement with those reported in the literature.[8]

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-1-acetoxy-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl acetate 4,5-cyclic sulfate 40 and 43. Diol (187 mg, 0.65 mmol) was dissloved in dry CCl_4 (2.5 ml) and thionyl chloride (85 µl, 1.17 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, then cooled to 0 °C and CH_3CN (2.5 ml), $RuCl_3.3H_2O$ (1.4 mg, 0.007 mmol), $NaIO_4$ (250 mg, 1.17 mmol) and water (3.75 ml) were added. The mixture was stirred for 30 min at 0 °C then 5 min at room temperature and diluted with ether (50 ml). The organic layer was washed with water (7 ml), saturated aqueous sodium bicarbonate (10 ml), dried over magnesium sulfate and the solvent evaporated to yield a pale yellow oil which was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent to afford:
(i).*(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-1-acetoxy-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl acetate 4,5-cyclic sulfite* as a colourless oil (36 mg, 17%); IR (neat): ν (cm^{-1}) 2974 (s), 2876 (s), 1732 (C=O), 1372, 1238 (C-O-C asym.), 1202 (O_2SO), 1045 (C-O-C sym.); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.92 (3H, t, $J_{2'',1''}$ 7.3 Hz, $CH_2C\underline{H}_3$), 1.16 (3H, s, 2'-Me), 1.36, 1.38* (3H, d, $J_{6,5}$ 6.5 Hz, H-6), 1.46-2.10 (10H, m, CH_2), 2.02 (3H, s, CH_3CO), 3.70-3.90 (3H, m, CH_2O, H-5), 4.75-4.90 (1H, m, H-1); MS (CI, CH_4): *m/z* (%) 335 (M+H, 10), 275 (M-$C_2H_3O_2$, 31), 211 (M-$C_2H_3O_4S$, 100), 193 (M-$C_2H_5O_5S$, 43) and 85 (M-$C_{10}H_{17}O_5S$, 23); HRMS: calculated for $C_{15}H_{27}O_6S$ $(M+H)^+$, 335.1528, found 335.1528.
(ii).*(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-1-acetoxy-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl 4,5-cyclic sulfate* **40** and **43.** as a colourless oil (147 mg, 65%); IR (neat): ν (cm^{-1}) 2966 (s), 2872, 1738 (C=O), 1454 (O_2SO_2), 1372, 1234 (C-O-C), 1210 (O_2SO_2), 1045 (C-O-C sym.); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.98 (3H, t, $J_{2'',1''}$ 7.4 Hz, $CH_2C\underline{H}_3$), 1.13 (3H, s, 2'-Me), 1.42, 1.43* (3H, d, $J_{6,5}$ 6.5 Hz, H-6), 1.40-2.10 (10H, m, CH_2), 2.04, 2.04* (3H, s, CH_3CO), 3.65-3.90 (3H, m, CH_2O, H-5), 4.78 (0.5H, dd, $J_{1,2A}$ 9.7, $J_{1,2B}$ 2.5 Hz, H-1), 4.87* (0.5H, dd, $J_{1,2A}$ 6.6, $J_{1,2B}$ 2.2 Hz, H-1); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.1, 7.4* (CH_3, C-2''), 13.8 (CH_3, C-6), 20.8 (CH_3, CH_3CO), 21.8, 21.9* (CH_3, 2'-Me), 23.3 (CH_2), 24.8 (CH_2), 25.6 (CH_2), 30.3 (CH_2), 34.7 (CH_2), 68.2 (CH_2, C-5'), 76.8, 76.9* (CH, C-1), 83.2 (quat., C-2'), 84.3, 84.4* (CH, C-5), 97.4 (quat., C-4), 170.6 (quat., C=O); MS (CI, CH_4): *m/z* (%) 351 (M+H, 14), 291 (M-$C_2H_3O_2$, 93), 193 (M-$C_2H_5O_6S$, 100) and 85 (M-$C_{10}H_{17}O_6S$, 44); HRMS: calculated for $C_{15}H_{27}O_7S$ $(M+H)^+$, 351.1477, found 351.2524.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-(4''-methoxybenzyloxy)-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl cyclic sulfite 36 and 38. Thionyl chloride (33 µl, 0.46 mmol) was added dropwise over 5 min, to a mixture of diols **23** and **26** (139 mg, 0.38 mmol) and triethylamine (114 µl, 0.82 mmol) dissolved in ether (7 ml) at 0 °C. The reaction mixture was stirred at this temperature for 2 h, and diluted with ether (7 ml). The organic layer was washed with water (2 x 5 ml), dried over magnesium sulfate and the solvent removed under reduced pressure to afford a yellow oil which was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent to afford a mixture of cyclic sulphites **36** and **38** (139 mg, 88%) as a colourless oil; IR (neat): ν (cm^{-1}) 2970, 2871, 1248 (C-O-C), 1209 (O_2SO), 1096, 1038 (C-O-C); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.91, 0.99* (3H, t, $J_{2'',1''}$ 7.3 Hz, $CH_2C\underline{H}_3$), 1.15 (3H, s, 2'-Me), 1.43, 1.46* (3H, d, $J_{6,5}$ 6.7 Hz, H-6), 1.21-2.10 (10H, m, CH_2), 3.27 (1H, m, H-5), 3.79 (3H, s, OMe), 3.75-3.95 (3H, m, CH_2O, H-1), 4.49 (1H, d, $J_{HA,HB}$ 11 Hz, $C\underline{H}_ACH_BAr$), 4.66-4.82 (1H, m, $CH_AC\underline{H}_BAr$), 6.87 (2H, d, *J*

8.6 Hz, Ar-H), 7.25 (2H, d, *J* 8.6 Hz Ar-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.5, 7.8* (CH_3, C-2"), 13.4, 13.6* (CH_3, C-6), 23.6, 23.9* (CH_3, 2'-Me), 25.9 (CH_2), 26.4, 26.5* (CH_2), 31.0, 31.5* (CH_2), 32.0, 32.3* (CH_2), 33.1, 33.4* (CH_2), 55.2 (CH_3, OMe), 67.8 (CH_2, C-5'), 74.3 (CH_2, CH_2Ar), 78.4 (CH, C-5), 84.2 (CH, C-1), 86.0, 86.1* (quat., C-2'), 94.9, 95.0* (quat., C-4), 113.7 (CH, C-3'''), 129.5 (CH, C-2'''), 131.1 (quat., C-1'''), 159.1 (quat., C-4'''); MS (CI, CH_4): *m/z* (%) 411 (M-H, 6), 305 (M-C_8H_{11}, 11), 241 (M-$C_8H_{21}O_2S$, 21), 211 (M-$C_8H_9O_4S$, 25), 121 (M-$C_{13}H_{23}O_5S$, 100) and 85 (M-$C_{16}H_{23}O_5S$, 11); HRMS: calculated for $C_{21}H_{33}O_6S$ $(M+H)^+$, 413.1997, found 413.1998.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-hydroxy-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl cyclic sulfite 37 and 39. DDQ (186 mg, 0.82 mmol) was added to a mixture of ethers **36** and **38** (169 mg, 0.4 mmol) in water (0.4 ml)) and dichloromethane (8 ml) at 0 °C. The reaction mixture was stirred at this temperature for 130 min. Sodium bicarbonate (100 mg, 1.19 mmol) followed by water (8 ml) was added and the aqueous layer extracted with dichloromethane (3 x 10 ml). The organic layers were combined, dried over magnesium sulfate and the solvent evaporated to yield an orange oil which was purified by flash chromatography using hexane/ethyl acetate (4:1), then (1:1), as eluent to afford a mixture of cyclic sulphites **37** and **39** (114 mg, 95%) as a colourless oil; IR (neat): ν (cm^{-1}) 3558 (b, OH), 2971 (s), 2873 (s), 1248 (C-O-C asym.), 1208 (O_2SO), 1044 (C-O-C sym.); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.92, 1.00* (3H, t, $J_{2'',1''}$ 7.4 Hz, $CH_2C\underline{H}_3$), 1.07 (3H, s, 2'-Me), 1.20-2.21 (13H, m, CH_2, H-6), 3.41 (1H, m, H-1), 3.69-3.88 (3H, m, CH_2O), 4.41, 4.79* (1H, m, H-5); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.6, 7.9* (CH_3, C-2"), 13.2, 13.6* (CH_3, C-6), 23.0, 23.1* (CH_3, Me-2'), 23.8, 24.7* (CH_2), 26.1 (CH_2), 30.5, 30.7* (CH_2), 36.6 (CH_2), 40.8 (CH_2), 67.6, 67.9* (CH_2, C-5'), 78.0 (CH, C-5), 79.9 (quat., C-2'), 85.8 (CH, C-1), 95.1 (quat., C-4); MS (CI, CH_4): *m/z* (%) 275 (M-OH, 14), 229 (M+H-O_2S, 29), 211 (M-SO_3H, 100), 193 (16), and 85 (M-$C_{18}H_{15}O_4S$, 16); HRMS: calculated for $C_{13}H_{25}O_5S$ $(M+H)^+$, 293.1422, found 293.1422.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-(4''-methoxybenzyloxy)-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl cyclic sulfate 41 and 44. Thionyl chloride (96 μl, 1.32 mmol) was added to a mixture of diols **23** and **26** (241 mg, 0.66 mmol) in CCl_4 (1.9 ml) and the reaction mixture stirred at room temperature for 2 h under an atmosphere of nitrogen. The reaction mixture was cooled to 0 °C and CH_3CN (1.9 ml), $RuCl_3.3H_2O$ (1.9 mg, 0.01 mmol), $NaIO_4$ (282 mg, 1.32 mmol) and water (2.85 ml) were added. Stirring was continued at 0 °C for 30 min then at room temperature for 2 h after which ether (40 ml). was added. The organic layer was separated, washed sequentially with water (7 ml) and saturated aqueous sodium bicarbonate (10 ml), dried over magnesium sulfate and the solvent evaporated to yield a pale yellow oil which was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent to afford a mixture of cyclic sulphates **41** and **44** (169 mg, 60%) as a colourless oil; IR (neat): ν (cm^{-1}) 2967, 2873, 1454 (O_2SO_2), 1251 (C-O-C), 1210 (O_2SO_2), 1097, 1040 (C-O-C); ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.97, 1.01* (3H, t, $J_{2'',1''}$ 7.5 Hz, $CH_2C\underline{H}_3$), 1.27, 1.27* (3H, s, 2'-Me), 1.41, 1.46* (3H, d, $J_{6,5}$ 6.8 Hz, H-6), 1.49-2.11 (10H, m, CH_2), 3.47 (1H, q, *J* 6.8 Hz, H-5), 3.86 (3H, s, OMe), 3.73-3.88 (3H, m, CH_2O, H-1), 4.87-4.98 (1H, m, $C\underline{H}_ACH_BAr$), 5.03-5.14 (1H, m, $CH_AC\underline{H}_BAr$), 6.93 (2H, d, *J* 8.9 Hz, Ar-H), 7.99 (2H, d, *J* 8.9 Hz Ar-H); ^{13}C NMR (50 MHz; $CDCl_3$): δ 7.3 (CH_3, C-2"), 13.9 (CH_3, C-6), 22.1 (CH_3, 2'-Me), 23.8 (CH_2), 25.1 (CH_2), 25.8 (CH_2), 30.5 (CH_2), 35.3 (CH_2), 55.5 (CH_3, OMe), 68.3, 68.4* (CH_2, C-5'), 77.6 (CH_2, CH_2Ar), 83.6 (CH, C-5), 83.9 (quat., C-2'), 84.3 (CH, C-1), 97.5 (quat., C-4), 113.8 (CH, C-3'''), 122.0 (quat., C-1'''), 131.7 (CH, C-2'''),

163.6 (quat., C-4'''); MS (CI, CH_4): *m/z* (%) 443 (M+CH_3, 13), 345 (M-C_5H_7O, 41), 291 (M-$C_8H_9O_2$, 41), 193 (M-$C_{14}H_{19}O_3$, 100), and 85 (M-$C_{16}H_{23}O_6S$, 55); HRMS: calculated for $C_{21}H_{33}O_7S$ $(M+H)^+$, 429.1946, found 429.2624.

(1R*, 2'S*, 4R*, 5R*)- and (1R*, 2'S*, 4S*, 5S*)-4-Ethyl-1-hydroxy-1-(2'-methyltetrahydrofur-2'-yl)hexa-4,5-diyl cyclic sulfate 42 and 45. DDQ (198 mg, 0.87 mmol) was added to a mixture of cyclic sulfates **41** and **44** (169 mg, 0.4 mmol) in water (0.4 ml) and dichloromethane (8 ml) at 0 °C. The reaction mixture was stirred at this temperature for 2 h. Saturated sodium bicarbonate (8 ml) was added and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The organic layers were combined, dried over magnesium sulfate and the solvent evaporated to yield an orange oil which was purified by flash chromatography, using hexane/ethyl acetate (4:1) and then (1:1) as eluent to afford a mixture of cyclic sulphates **42** and **45** (90 mg, 74%) as a colourless oil; IR (neat): ν (cm^{-1}) 3444 (b, OH), 2974, 2874, 1454 (O_2SO_2), 1248 (C-O-C), 1209 (O_2SO_2), 1043 (C-O-C); ^1H NMR (200 MHz; $CDCl_3$): δ 0.99 (3H, t, $J_{2'',1''}$ 7.5 Hz, $CH_2C\underline{H}_3$), 1.10 (3H, s, 2'-Me), 1.44, 1.47* (3H, d, $J_{6,5}$ 6.5 Hz, H-6), 1.20-2.28 (10H, m, CH_2), 2.69 (1H, s, OH), 3.45 (1H, dd, *J* 10.4, *J* 2.0 Hz, H-1), 3.71-3.92 (2H, m, CH_2O), 4.91, 4.99* (1H, q, $J_{5,6}$ 6.5 Hz, H-5); MS (CI, CH_4): *m/z* (%) 291 (M-OH, 26), 229 (M+H-O_3S, 54), 211 (M+H-SO_4, 100), 193 (44), and 85 (34); HRMS: calculated for $C_{13}H_{25}O_5S$ $(M+H)^+$, 309.1371, found 309.1361.

Base induced cyclisation of cyclic sulfates 42 and 45. Sodium hydride (4 mg, 0.2 mmol) was cooled to 0 °C and ethanol (2.0 mL) added. A mixture of cyclic sulfates **42** and **45** (38 mg, 0.1 mmol) in ethanol (2 mL) was cooled to 0 °C and added dropwise to the sodium ethoxide solution. The resultant suspension was stirred overnight, allowing the reaction to warm to room temperature. Ethanol was removed under reduced pressure to afford a colourless oil which was diluted with ether (4 mL) and treated with 20% H_2SO_4 for 24 h. The organic layer was separated and the aqueous layer extracted with ether. The organic layers were combined, washed with aq. K_2CO_3, dried over magnesium sulfate and the solvent evaporated to yield a yellow oil. Further purification by flash chromatography using hexane/ethyl acetate (9:1), then (4:1) as eluent afforded:
(i). a mixture of tetrahydrofurans **33** and **34** (5 mg, 18%) for which the ^1H NMR, IR and mass spectrometry data were in agreement with the literature.[8]
(ii). *(2S*, 6R*, 2'S*)- and (2R*, 6R*, 2'S*)-3-Ethyl-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)-5,6-dihydro-2H-pyran* **46** and **47** (8 mg, 28%) as a colourless oil;IR (neat): ν (cm^{-1}) 2927, 2867, 1458, 1375, 1260 (C-O-C), 1070 (C-O-C); ^1H NMR (200 MHz; $CDCl_3$): δ 1.03 (3H, t, $J_{2'',1''}$ 7.4 Hz, $CH_2C\underline{H}_3$), 1.27 (3H, s, 2'-Me), 1.18-2.25 (11H, m, 4 x CH_2, 2-Me), 3.25 (1H, dd, $J_{6,5A}$ 5.3, $J_{6,5B}$ 11.0 Hz, H-6), 3.49 (1H, q, $J_{2,2\text{-}Me}$ 7 Hz, H-2), 3.80-4.00 (2H, m, CH_2O), 5.50 (1H, m, H-4); MS (CI, CH_4): *m/z* (%) 225 (M+CH_3, 56), 209 (M-H, 100), 113 (M-C_7H_{13}), 85 (M-$C_8H_{13}O$); HRMS: calculated for $C_{13}H_{21}O_2$ $(M-H)^+$, 209.1541, found 209.1534.

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